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Age–period–cohort analyses of breast-, ovarian-, endometrial- and cervical-cancer mortality rates for Caucasian women in the USA

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Background Age–period–cohort analyses of US breast-cancer mortality rates reveal an unexpected decrease in risk for women born after 1948. Hormones are thought to play an important role in the aetiology of breast cancer and female gynaecologic cancers, and thus the evaluation of birth-cohort trends for female gynaecologic cancers may shed light on the declining breast-cancer risk among 'baby-boomers'.

Methods Age–period–cohort analyses are applied to US mortality rates for breast cancer, ovarian cancer, endometrial cancer and cervical cancer from 1950 through 1995.

Results Age–period–cohort analyses provide no clues regarding the declining birth-cohort risk for breast cancer in 'baby-boomers'. The birth-cohort curves for ovarian and endometrial cancers are roughly similar, and largely explained by known risk factors. The calendar-period curve for endometrial cancer reveals increased risk between 1960 and 1980, probably due to increased use of oestrogen replacement therapy. Changes in the birth-cohort curve for cervical cancer reflect, for the most part, changes in sexual activity. An unexpected significant increase in the calendar-period curve for ovarian cancer occurred around 1980.

Conclusion Most of the major changes in the calendar-period and birth-cohort curves for breast cancer and female gynaecologic cancers can be explained by documented changes in known risk factors and in medical practice. The decreasing breast-cancer birth-cohort risk among 'baby-boomers' and the increasing ovarian-cancer calendar-period curve after 1980 are recent changes that require further investigation.

Keywords age–period–cohort model, breast cancer, ovarian cancer, endometrial cancer, cervical cancer.

Introduction

Evaluations of trends in US breast-cancer rates have consistently demonstrated marked variation in risk by birth cohort[1–5]. For women born from 1910 through about 1940, US birth-cohort trends in breast-cancer risk could be explained largely by childbearing patterns[4,6]. The birth-cohort trend in risk after 1940, however, has shown a clear departure from the risk-pattern expected based on trends in known and suspected risk factors. In particular, there has been a dramatic and significant decrease in birth-cohort risk for women born after 1948 (i.e. 'baby-boomers'), a period in which increasing breast-cancer risk would be expected, because of decreasing parity and increasing age at first birth[7,8]. A similar unexplained, marked decrease in birth-cohort risk of breast cancer among baby-boomers has been reported in Scotland[9–11].

The importance of endogenous and exogenous hormones in breast-cancer aetiology[12,13] suggests that it might be informative to examine trends in other female cancers that show possible aetiological involvement of hormones. Accordingly, we have investigated trends in mortality rates for ovarian, endometrial and cervical cancer among US Caucasian women, using age–period–cohort methods[10,14–16]. The calendar-period and birth-cohort trends for these cancers are compared and contrasted with those for breast cancer, and the implications with regard to improvements in medical interventions and changes in risk factors are discussed.

Methods

The cancer mortality data are from the National Center for Health Statistics (NCHS, 6525 Belcrest Rd, Hyattsville, MD 20782, USA), which receives death

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certificates from each state and compiles mortality data by race, sex, age, year and cause of death. For the current study, only Caucasian females in the USA who were reported to have an underlying cause of death of breast, ovarian, cervical or endometrial cancer between 1950 and 1995 were included. The sites were as coded on the death certificates according to the *Manual of International Statistical Classification of Diseases, Injuries, and Causes of Death* (ICD). The sixth revision of the manual[17] was used for deaths in 1950–57; the seventh[18] for 1958–67; the eighth[19] for 1968–78 and the ninth[20] from 1979–95. The classification of anatomic sites for each cancer was made consistent with the mortality data available since 1950[21]. Breast-cancer mortality data include the sites breast, mammary gland, nipple, and Paget's disease of the breast and nipple, and are designated by ICD 6th revision, 170; 7th revision, 170; 8th and 9th revisions, 174. Cervical-cancer mortality data include the sites uterine cervix and external os of the uterus, and are designated by ICD 6th revision, 171; 7th revision, 171; 8th and 9th revisions, 180. Endometrial-cancer mortality data include the sites fundus and body of the uterus, and are designated by ICD 6th revision, 172; 7th revision, 172; 8th revision, 182.0 and 9th revision, 182.0–182.1. Ovarian-cancer mortality data include the sites broad ligaments, Fallopian tube, ovary, oviduct and uterine ligament, and are designated by ICD 6th revision, 175; 7th revision, 175.0–175.9; 8th revision, 183.0–183.9 and 9th revision, 183.0–183.9.

Let R_{ijk} denote the mortality rate for the ith of A age intervals in the jth of P calendar year periods, where $k = A + j - i$ indexes the corresponding birth cohort. In this notation, there are $C = A + P - 1$ birth cohorts, with larger values of k corresponding to more recent birth cohorts. The standard age–period–cohort analysis is based on Poisson regression with the log-linear model,

$$\log[E(R_{ijk})] = \alpha_i + \pi_j + \gamma_k \qquad (1)$$

where α_i are the age effects, π_j are the calendar-period effects and γ_k are the birth-cohort effects.

Age–period–cohort models were fitted to the cancer mortality data for each site, breast, cervix, endometrium and ovary, using 2-year age and calendar-period intervals[6]. For breast, cervix and ovary, there were 30 age intervals, ranging from 24–25 years of age to 82–83 years of age; 23 calendar-period intervals, ranging from 1950–51 to 1994–95; and 52 4-year birth-cohort intervals, ranging from 1866–69 to 1968–71. For endometrium, there were 27 age intervals, ranging from 30–31 years of age to 82–83 years of age; 23 calendar-period intervals, ranging from 1950–51 to 1994–95; and 49 4-year birth-cohort intervals, ranging from 1866–69 to 1962–65. Seventy-five percent of the births within each 4-year birth cohort will have occurred in the middle 2 years. Each birth cohort will be referred to in the text by the second year in the interval. For example, the 1949 birth cohort will refer to women born from 1948 through 1951, with 75% of women in this cohort having been born in 1949 and 1950.

Changes in the slope of long-term linear trends in birth-cohort and calendar-period effects were examined using identifiable differences in linear contrasts[16]. The contrast in period effects given by:

$$C_p = 3\pi_{h+3} + \pi_{h+2} - \pi_{h+1} - 3\pi_h - (3\pi_h + \pi_{h-1} - \pi_{h-2} - 3\pi_{h-3}) \qquad (2)$$

was used to identify a change in the slope of the calendar-period effects at the calendar period denoted by h for breast, ovarian and cervical cancer. There was greater variability of the estimates for endometrial cancer; the contrast

$$C_p^* = 5\pi_{h+5} + 3\pi_{h+4} + \pi_{h+3} - \pi_{h+2} - 3\pi_{h+1} - 5\pi_h - (5\pi_h + 3\pi_{h-1} + \pi_{h-2} - \pi_{h-3} - 3\pi_{h-4} - 5\pi_{h-5}) \qquad (3)$$

was therefore used to examine the calendar-period slope for endometrial cancer. The contrast in birth-cohort effects given by

$$C_c = 3\gamma_{k+6} + 2\gamma_{k+5} + \gamma_{k+4} - \gamma_{k+2} - 2\gamma_{k+1} - 3\gamma_k - (3\gamma_k + 2\gamma_{k-1} + \gamma_{k-2} - \gamma_{k-4} - 2\gamma_{k-5} - 3\gamma_{k-6}) \qquad (4)$$

was used to identify a change in the slope of the birth-cohort effects at the birth cohort denoted by k. In analyses of cancer mortality data, a significant change in the birth-cohort trend usually indicates changes in an aetiologic factor resulting in increasing or decreasing risk. A significant change in the calendar-period trend often indicates the impact of newly-introduced or improved medical interventions, or a change in ascertainment or coding of cause of death. Standard errors (SE) of the linear contrasts were adjusted for possible over-dispersion whenever the deviance exceeded the number of residual degrees of freedom[22].

Results

The calendar-period and birth-cohort effects for breast-cancer mortality are shown in Figure 1. Previously published curves for breast cancer were based on analyses of rates only since 1969[7,8]. The calendar-period curve for breast cancer had two major changes of direction. The slope of the calendar-period trend increased around

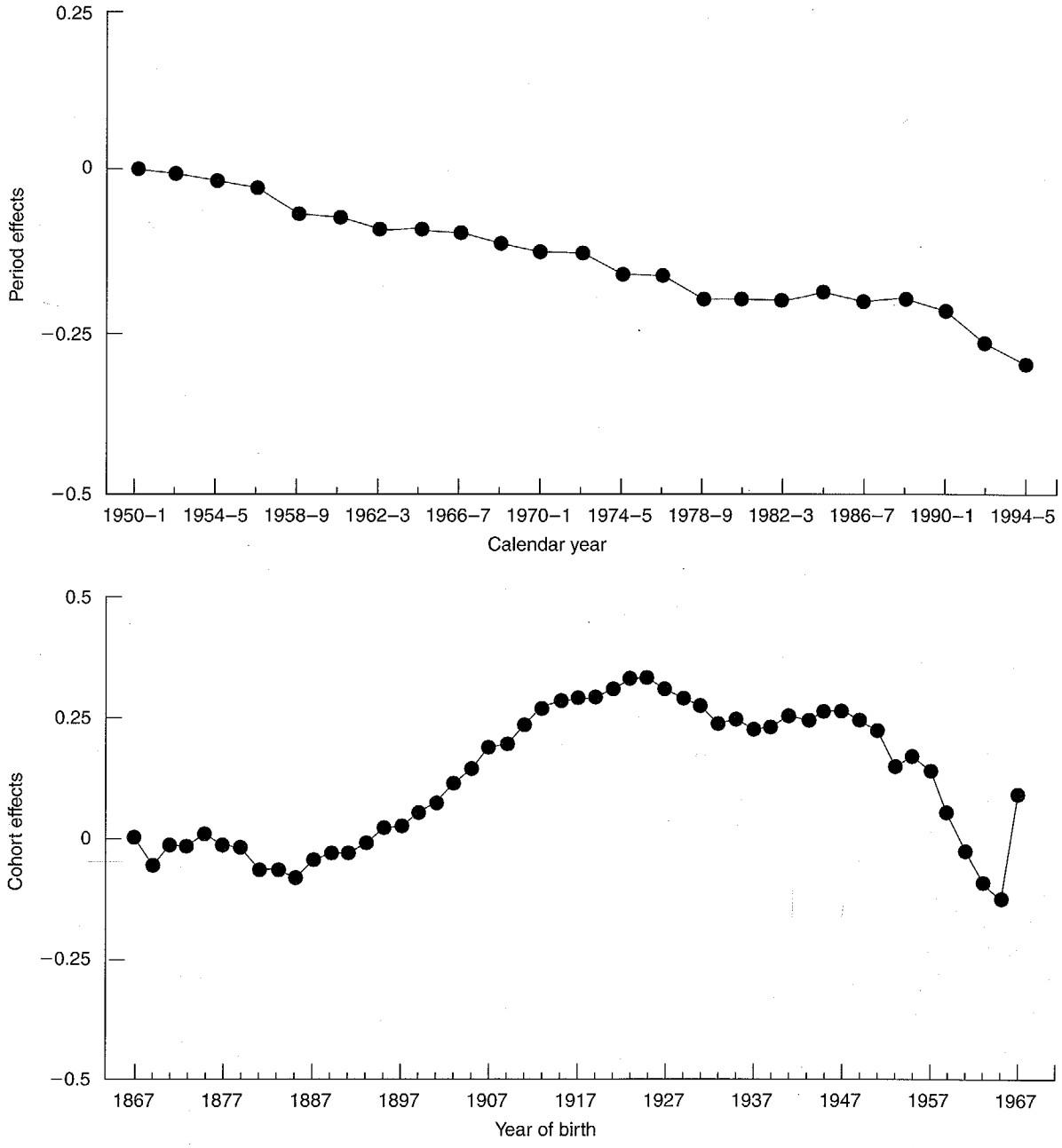

Fig. 1 *Maximum likelihood estimates of 2-year calendar-period effects* ***(top panel)*** *and 4-year birth-cohort effects, labelled by second year* ***(bottom panel),*** *for an age–period–cohort model fit to breast-cancer mortality data for US Caucasian women. The estimates were obtained under the constraint that the final birth-cohort effect is zero. The relationship between year of birth, year of death and age at death is linear, therefore a constraint must be imposed in order to obtain estimates. Changes in the slope of the calendar-period effect curve, or the birth-cohort effect curve are independent of the chosen constraint and thus provide unequivocal evidence of changes in risk. The final constrained birth-cohort effect is not plotted. The ratio of the deviance to the residual degrees of freedom was 1.8.*

1980 [C_p = 0.250; 95% confidence interval (CI) 0.166–0.334] and decreased in the late 1980s (C_p = −0.337; 95% CI −0.416 to −0.258). The birth-cohort curve for breast cancer had several changes in slope. There were increases in the slope of the birth-cohort curve in the mid-1880s (C_c = 0.859; 95% CI 0.650–1.068) and in the mid-1930s (C_c = 0.633; 95% CI 0.451–0.816). There were decreases in the slope of the birth-cohort curve around 1915 (C_c = −0.597; 95% CI −0.689 to −0.505), in the mid-1920s (C_c = −0.865; 95% CI −0.978 to −0.753), and in the late-1940s (C_c = −1.380; 95% CI −1.955 to −0.804).

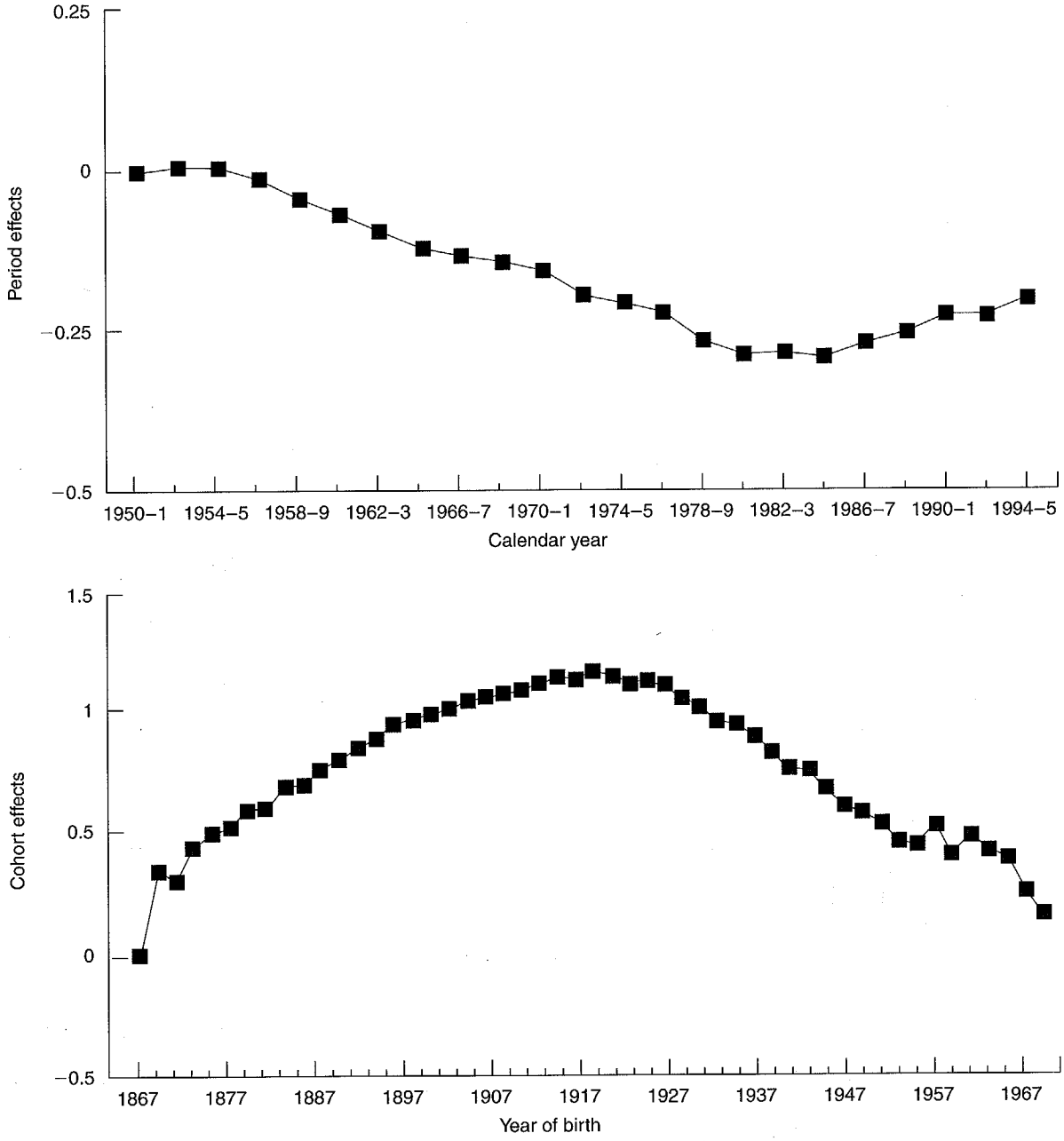

Fig. 2 *Maximum likelihood estimates of 2-year calendar-period effects* ***(top panel)*** *and 4-year birth-cohort effects, labelled by second year* ***(bottom panel),*** *for an age–period–cohort model fit to ovarian-cancer mortality data for US Caucasian women (see Figure 1 for details). The ratio of the deviance to the residual degrees of freedom was 1.3.*

The calendar-period and birth-cohort effects for ovarian-cancer mortality are shown in Figure 2. The calendar-period curve for ovarian cancer had two significant slope changes; the slope decreased around 1956 ($C_p = -0.251$; 95% CI −0.401 to −0.102) and increased around 1980 ($C_p = 0.332$; 95% CI 0.207–0.457). The US birth-cohort curve for ovarian cancer had significant decreases in slope around 1895 ($C_c = -0.628$; 95% CI −0.826 to −0.430), 1915 ($C_c = -0.889$; 95% CI −1.032 to −0.746) and around 1925 ($C_c = -1.035$; 95% CI −1.226 to −0.844). The ovarian-cancer birth-cohort curve had a significant increase around 1950 ($C_c = 1.110$; 95% CI 0.167–2.053).

The calendar-period and birth-cohort effects for endometrial-cancer mortality are shown in Figure 3. The calendar-period curve for endometrial cancer had a significant increase in slope around 1960 ($C_p^* = 1.870$; 95% CI 1.252–2.489) and a significant decrease in slope

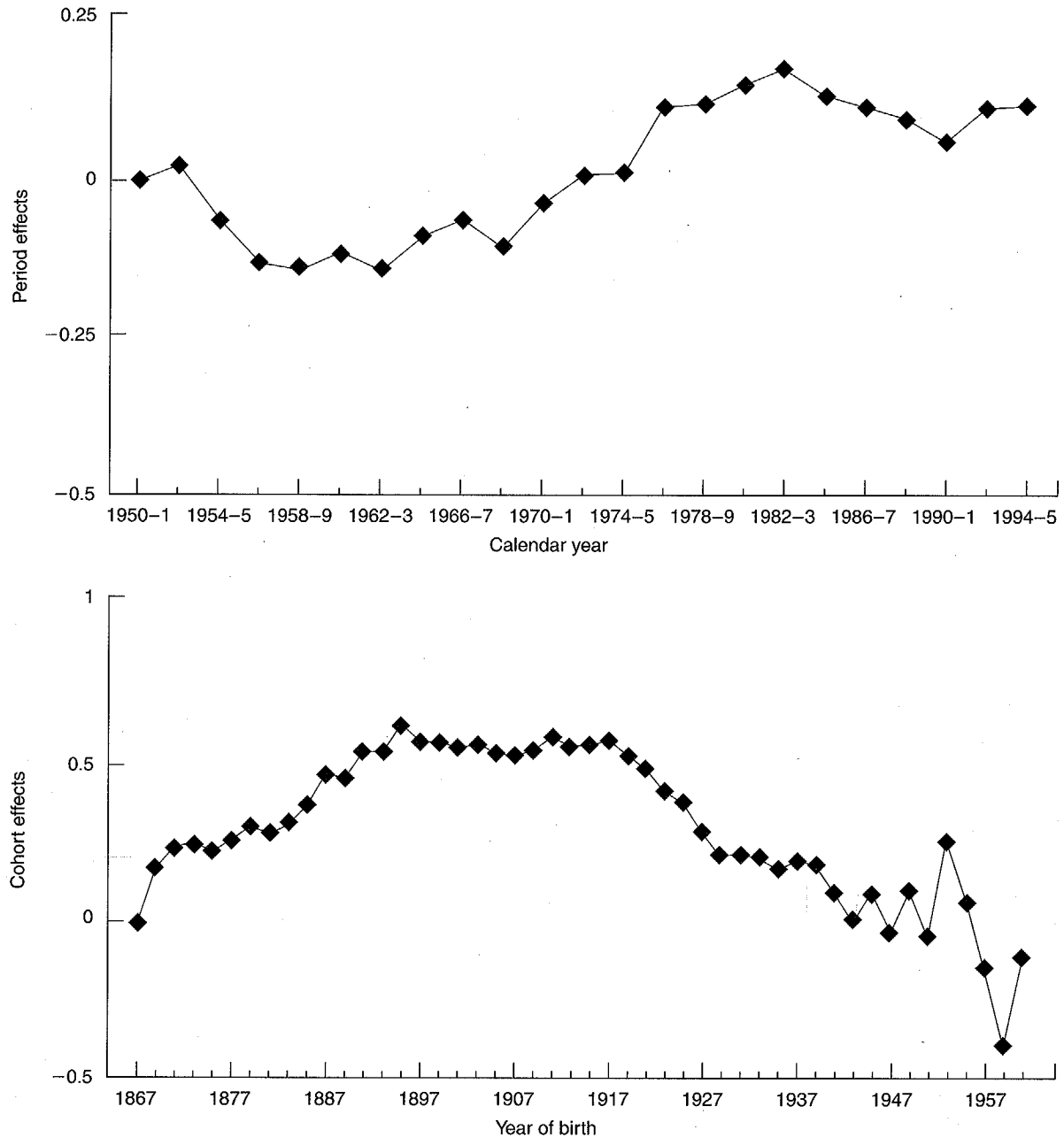

Fig. 3 *Maximum likelihood estimates of 2-year calendar-period effects* ***(top panel)*** *and 4-year birth-cohort effects, labelled by second year* ***(bottom panel),*** *for an age–period–cohort model fit to endometrial-cancer mortality data for US Caucasian women (see Figure 1 for details). The ratio of the deviance to the residual degrees of freedom was 1.2.*

around 1980 ($C_p^* = -2.097$; 95% CI −3.027 to −1.167). The birth–cohort curve for endometrial cancer had significant decreases in slope around 1895 ($C_c = -1.755$; 95% CI −2.133 to −1.376) and 1915 ($C_c = -1.902$; 95% CI −2.222 to −1.581). The birth-cohort curve for endometrial cancer had a significant increase in slope around 1930 ($C_c = 1.271$; 95% CI 0.643–1.899) and a large, but not statistically significant, increase in slope in the mid-1940s ($C_c = 1.366$; 95% CI −0.333–3.063).

The calendar-period and birth-cohort effects for cervical-cancer mortality are shown in Figure 4. The calendar-period curve had a significant decrease in slope in the early 1960s ($C_p = -0.495$; 95% CI −0.643 to −0.347) and a significant increase in slope around 1980 ($C_p = 0.363$; 95% CI 0.157–0.569). The birth-cohort curve had a decrease in slope around 1880 ($C_c = -0.580$; 95% CI −1.068 to −0.092) and had increases in slope around 1930 ($C_c = 0.857$; 95% CI 0.545–1.169)

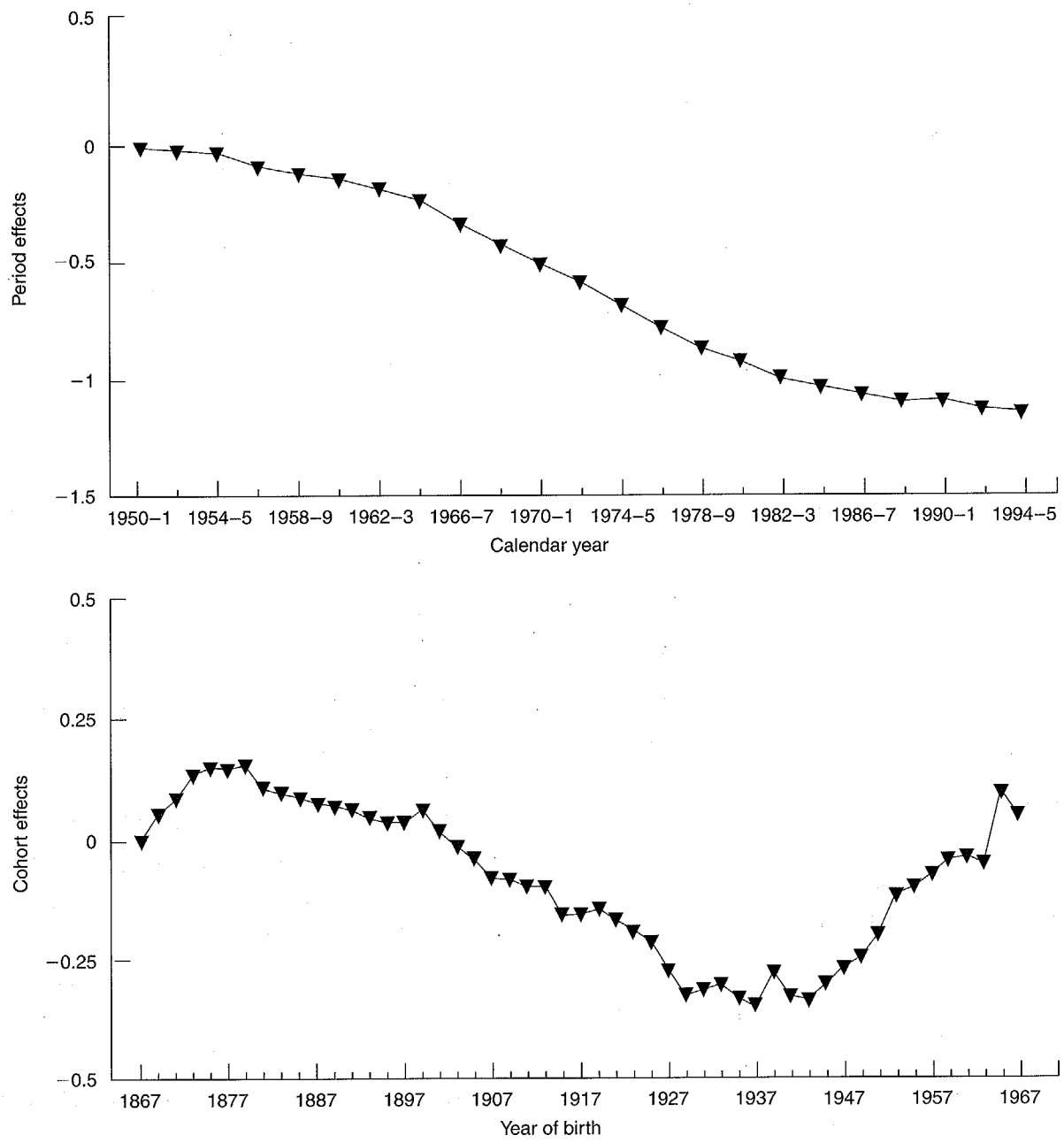

Fig. 4 *Maximum likelihood estimates of 2-year calendar-period effects* ***(top panel)*** *and 4-year birth-cohort effects, labelled by second year* ***(bottom panel),*** *for an age–period–cohort model fit to cervical-cancer mortality data for US Caucasian women (see Figure 1 for details). The ratio of the deviance to the residual degrees of freedom was 1.2.*

and in the mid-1940s (C_c = 1.218; 95% CI 0.785–1.650).

The age effects for all four types of cancer are shown in Figure 5. All four curves show the reduction in slope in older ages expected of cancers related to ovarian hormones. The ages at which the slopes change vary among the cancers; the slope decreases before age 40 for breast and cervical cancer (neither curve is linear under the age of 44, but both are fairly linear thereafter), around age 50 for ovarian cancer, and around age 60 for endometrial cancer.

Discussion

The calendar-period and birth-cohort curves for breast cancer in Figure 1 extend those presented earlier based on a shorter time-series of rates. The extended calendar-period curve provides no new information on changes in slope. As noted previously[7], the increased risk of death

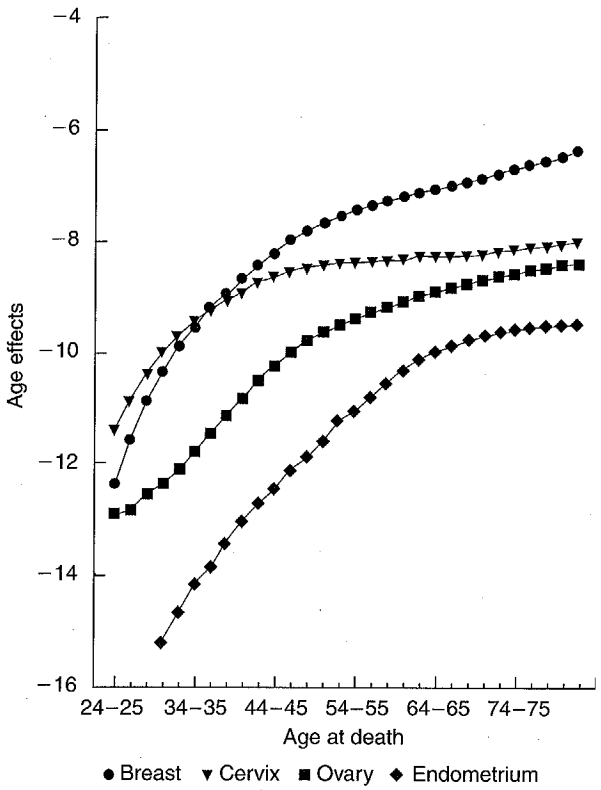

Fig. 5 Maximum likelihood estimates of age effects for age–period–cohort models fit to breast-, ovarian-, endometrial- and cervical-cancer mortality data for US Caucasian women (2-year age groups).

in the 1980s probably reflects the substantial increase in the number of breast-cancer diagnoses in the 1980s that resulted from the rapid expansion in the use of mammography during this decade[23,24]. The decreased risk of death beginning in the late 1980s reflects the benefits of both earlier detection and better adjuvant therapy[25]. The marked effects of improved treatment on mortality rates beginning in the late 1980s have been noted in other countries[7,26–28].

Changes in the breast-cancer birth-cohort curve are dramatic and appear to be related, at least in part, to changes in childbearing patterns. A plot of the proportion of nulliparous Caucasian women aged 20–24 years in the USA (Figure 6a), shows decreases in the age at first birth (i.e. increases in fertility), around 1913 and 1925. These decreases are consistent with the decreases in slope of the birth-cohort curve in breast-cancer risk around 1915 and 1925[7]. This latter change probably reflects increased fertility after World War II. However, the childbearing pattern after World War II indicates that breast-cancer risk should have continued falling for women born during the period through 1940, and then increased for an extended period.

This extended increase would have coincided with fertility rates beginning to fall with the entry of greater numbers of women into the workplace and the increased use of oral contraceptives (OCs) among young women. The birth-cohort effects departed from this expected pattern, showing an initial increase in slope in the mid-1930s (earlier than expected) and then a sharp decrease in slope in the late 1940s (contrary to the expected increase). The increase in risk in the mid-1930s could reflect the use of early, high dose OCs by women in their late twenties and thirties wanting to limit the size of their families. The decrease in risk in baby-boomers, however, has no plausible explanation.

It is of interest to note that the plot of nulliparity rates in young women (Figure 6a) indicates an increase in the age at first birth, beginning around 1905, that is not reflected by an increase in the breast-cancer birth-cohort slope. As noted by MacMahon[2], breast-cancer rates in the late 1800s and around the turn of the century appear to have departed from the pattern expected, based on fertility rates. The parity curves (Figure 6b) and nulliparity rates (Figure 6a) indicate different fertility trends prior to 1905, however, suggesting that fertility changes for women born late in the nineteenth century and early in the twentieth century may have been complex. Dietary restrictions during the Great Depression (1930s) may also have impacted on breast-cancer risk for some cohorts of women born during the first third of the century.

The initial decline in the ovarian-cancer calendar-period slope should be interpreted with caution, because of the lack of data prior to 1950, but it appears that a change in the diagnosis or treatment of ovarian cancer occurred in the mid-1950s that led to improved survival for ovarian-cancer patients. The increase in the ovarian-cancer calendar-period slope around 1980 is disturbing and is currently not understood. Ovarian-cancer incidence rates increased around 1980 (particularly among women aged ≥ 65 years)[29], but there was no apparent improvement in diagnostic technology for ovarian cancer in the 1980s to explain the increase in incidence. Ordinarily, changes in calendar-period slope for cancer mortality do not reflect changes in exposure to risk factors, but hormone exposures may provide exceptions to this rule (see the discussion of the endometrial-cancer calendar-period curve below). Oestrogen replacement formulations changed in the 1980s in response to an increased risk of endometrial cancer, but there is no evidence to suggest that the changes (e.g. combining progestins with oestrogens) would affect ovarian cancer.

The generally concave shape of the birth-cohort curve between 1880 and 1960 is remarkably similar to ovarian-cancer birth-cohort curves in Northern and

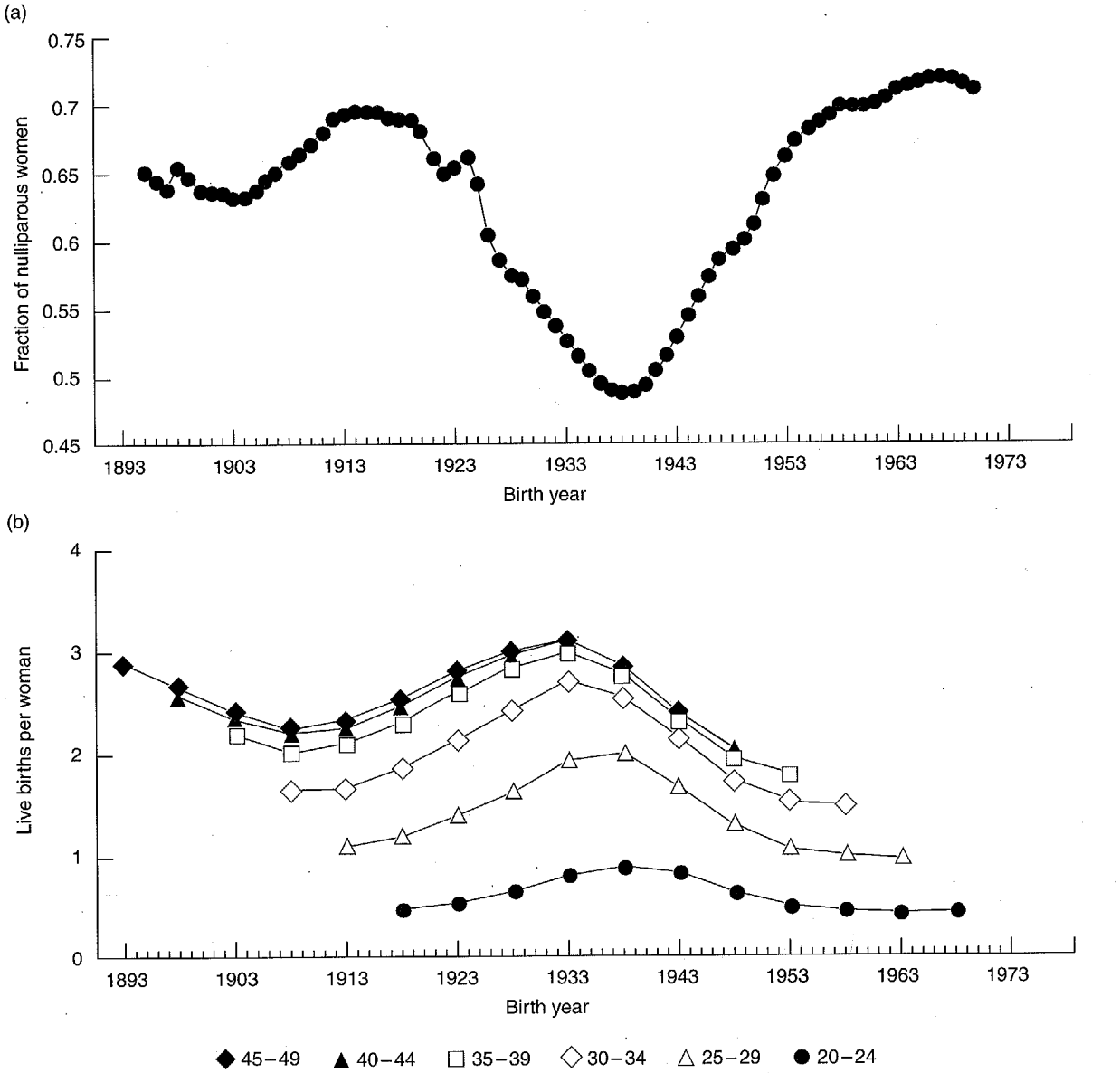

Fig. 6 (a) *Proportion of nulliparous Caucasian women aged 20–24 years in the USA plotted against birth cohort.* ***(b)*** *Mean number of live births per Caucasian woman in the USA plotted against birth cohort by 5-year age-group from 20–24 years of age through 45–49 years of age.*

Central European countries[30]. Parity is a strong protective factor for ovarian cancer[31,32]. Trends in family size have been shown to correlate with ovarian-cancer birth-cohort risk in England and Wales[33]. Figure 6b shows the parity curves for US Caucasian women. Parity in the USA decreased for women born from 1885 (the earliest year available) until around 1910. Parity began increasing rapidly for women born from around 1915 until the mid-1930s, and then decreased from the mid-1930s until at least 1960. The concave shape of the ovarian-cancer birth-cohort curve is consistent with parity trends through the mid-1930s. Between 1885 and 1935 there were three significant decreases in slope that occurred around 1895, 1915 and 1925. The latter decrease is consistent with the increase in childbearing after World War II. The 1915 decrease in the ovarian-cancer birth-cohort slope corresponds to the increase in parity occurring around 1913 (Figure 6b). Decreased caloric intake during the Great Depression may also have contributed to the simultaneous birth-cohort decreases in breast, ovarian and endometrial cancer around 1915.

The continued decrease in the ovarian-cancer birth-cohort curve after 1935, in spite of decreasing parity, probably reflects the beneficial effect of early OC use on ovarian-cancer risk[12,31,32]. The first users of OCs tended to be women who already had children, but

wanted to limit their family size. Both their early pregnancies and their subsequent use of OCs would have combined to lower their risk of ovarian cancer. Baby-boomers tended to avoid childbirth completely, or delay pregnancy for an extended period, largely by early use of OCs and their use for a long duration. The increase in the ovarian-cancer birth-cohort slope around 1950 may reflect a conflict between this adverse trend in childbearing patterns and the direct beneficial effects of OCs on ovarian-cancer risk, resulting in a continued decrease in ovarian-cancer rates, but with a slower rate of decrease. Attempts to model the joint effects of OC use and parity on the risk of ovarian cancer led to an underestimation of rates in older women[34]. This suggests that either the protective effects of OC use diminish with age, or that there is an additional risk factor in older women not accounted for in the model[34].

The increase in calendar-period risk for endometrial cancer was particularly sharp between 1968 and 1977. The increased calendar-period slope after 1960 and the subsequent decrease in the calendar-period slope around 1980 probably reflect the influence of hormone replacement therapy (HRT) on endometrial-cancer risk[12,35]. There was a four-fold increase in sales of oestrogens in the USA from 1962 to 1975[35–37]. Based on the number of oral noncontraceptive oestrogen prescriptions dispensed, it can be estimated that 4.5 million women, approximately 10% of women over the age of 30, could have been on HRT for the entire year of 1975[36]. The number of women actually taking oral oestrogens would have been higher, because not all women used oestrogens for the entire year. In addition, injectable oestrogens were used with about equal frequency as oral oestrogens in the 1970s[38]. From survey data it has been estimated that 20% of women who experienced menopause between 1970 and 1992 used HRT for ≥ 5 years[39]. The first published reports linking oestrogen use with endometrial cancer appeared in 1975[40,41], after which oestrogen prescriptions declined until lower doses of oestrogens, or combinations of progestins and oestrogens, replaced earlier formulations in the 1980s. In cancer studies, increased exposure to a risk factor does not usually result in a change in the calendar-period slope. The impact of oestrogen exposure on the endometrial-cancer calendar-period curve indicates that oestrogens affect a very late stage in the carcinogenesis process[42]. It is of interest to note that an effect of oestrogen replacement therapy on endometrial-cancer mortality rates had not previously been identified[35]; this demonstrates the power of age–period–cohort analyses.

For endometrial cancer, as for ovarian cancer, nulliparity is a risk factor and OC use (combination OCs only for endometrial-cancer) is a protective factor[35]. Thus it is perhaps not surprising that the birth-cohort curve for endometrial-cancer is somewhat similar to the birth-cohort curve for ovarian cancer. The endometrial-cancer birth-cohort curve, like the ovarian-cancer birth-cohort curve, had slope decreases in 1895 and 1915, the latter consistent with a documented increase in fertility. However, the decrease in slope around 1925, seen for both ovarian and breast cancer, and expected for endometrial cancer based on fertility patterns, is not observed for endometrial cancer. This may be, in part, a result of the high rate of misclassification of endometrial-cancer on death certificates. It is recognised that many deaths attributed to endometrial cancer on death certificates should actually have been classified as cervical cancer deaths[35,43,44]. Thus, the simultaneous slope increases observed for the endometrial-cancer and cervical-cancer birth-cohort curves around 1930 and 1945 may largely reflect risk-factor changes for cervical cancer, rather than for endometrial cancer. In addition, however, some increase in endometrial-cancer birth-cohort risk for women born in the 1930s, due to the high oestrogen doses in early, sequential OCs, can not be ruled out. Likewise, increasing obesity rates may be contributing to increasing endometrial-cancer risk in more recent birth cohorts.

The calendar-period curve for cervical cancer probably reflects the beneficial effect of early detection using Papanicolaou (Pap) smear screening. The slope decrease in 1962 coincides with a rapid increase in Pap smear screening after 1960; the number of Pap smear examinations per 100 women increased from 10 in 1961 to 26 in 1966[45]. The increase in the gradient of the calendar-period slope around 1980 may indicate a saturation effect; almost all women who are willing to be screened for cervical cancer may now be screened regularly by Pap smear.

Interpretation of the birth-cohort curve for cervical cancer is simplified by recent epidemiologic advances demonstrating that human papillomavirus (HPV) is the central causal agent for cervical cancer[46,47]. HPV is sexually transmitted, therefore changes in the birth-cohort curve should reflect changes in sexual behaviour. Indeed, the increase in sexual promiscuity in the baby-boom generation is reflected by an increase in the birth-cohort curve around 1945. The increase in the birth-cohort slope around 1930 may reflect increasing sexual activity after World War II, or it may reflect the introduction into the USA of new oncogenic forms of HPV by soldiers returning from the war. The Venereal Disease Program of the US Public Health Service documents a doubling of the number of reported cases of gonorrhea (excluding known military cases) from 1941 through 1947[48]. Similar increases in the cervical-cancer birth-cohort slope were observed in England and Wales, and in Scotland, and were shown to correlate with

increasing venereal-disease rates in the same birth cohorts, suggesting that increasing sexual activity was responsible[49]. It is unclear at this time what could explain the decrease in cervical-cancer birth-cohort slope around 1880. Information on trends in sexual activity during the nineteenth century are not readily available, so a reduction in sexual activity could not be verified. Introduction or increased use of prophylactic devices would be another possible explanation, but there are no indications of widespread use of condoms, or other prophylactic devices, until the twentieth century.

Although ovarian hormones play an important role in the natural histories of breast, ovarian and endometrial cancer, differences among the age-effect curves suggest that the relationship is complex. The different shapes of the risk curves by age for breast and endometrial cancer have been noted in an examination of age-specific incidence and mortality rates[50]. Breast involution begins well before menopause, so the early flattening of the breast-cancer age effect curve is not unexpected[51]. The reason that the risk of ovarian cancer diminishes around the time of menopause, while the risk of endometrial cancer doesn't change until at least 10 years later, is not fully understood.

Although many of the characteristics of the birth-cohort effect curves and calendar-period effect curves can be explained by changes in known risk factors, or changes in medical practices, there are some changes in the curves that remain unexplained. The decreases in birth cohort slope in 1895 for both endometrial cancer and ovarian cancer have no ready explanation, and there was no increase in the breast-cancer birth-cohort slope corresponding to an apparent increase in the age at first birth, beginning in 1905. Some recent changes remain unexplained; in particular, the declining birth-cohort risk for breast cancer in baby-boomers and the increasing calendar-period risk for ovarian cancer around 1980 require further investigation.

Note added in proof

Recent studies suggest that breast-cancer risk is increased more by oestrogen–progestin hormone replacement regimens than by oestrogen regimes [52–54]. Menopausal progestin use increased in the 1980s[55] and thus it is possible that the greater use of combined oestrogen–progestin replacement regimens contributed to the increase around 1980 in the slope of the calendar-period curve for breast cancer.

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